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# Effect of inhaled corticosteroids on bronchial asthma in Japanese athletes

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ABSTRACT

*Background:* Asthma has a higher prevalence in athlete populations such as Olympic athletes than in the general population. Correct diagnosis and management of asthma in athletes is important for symptom control and avoidance of doping accusations. However, few reports are available on asthma treatment in the athlete population in clinical practice. In this study, we focused on the clinical efficacy of inhaled corticosteroid (ICS) for asthma in a Japanese athlete population.

*Methods:* The study subjects included athletes who visited the Niigata Institute for Health and Sports Medicine, Niigata, Japan for athletic tests and who were diagnosed with asthma on the basis of respiratory symptoms and positive results in a bronchodilator or bronchial provocation test such as exercise, hypertonic saline, or methacholine provocation. The athletes received ICS alone for at least 3 months, and the clinical background, sports type, and treatment efficacy were analyzed.

*Results:* The study population comprised 80 athletes (59 men and 21 women) with a median age of 16.0 years. Regarding sports type, 28 athletes engaged in winter sports (35%), 22 in endurance sports (27.5%), and 25 in indoor sports (31.3%). Although ICS is the primary treatment in athlete asthma, 16.3% of the athletes showed an unsatisfactory response to treatment according to the Global Evaluation of Treatment Effectiveness (GETE). These subjects were characterized by a decreased response to methacholine and lower values for $FEV_1$/FVC and type 2 helper T cell (Th2)-associated biomarkers relative to responsive athletes. In multivariate analysis, $FEV_1$/FVC and the logarithm to the base 10 of the IgE level were independently associated with the ICS response.

*Conclusions:* These data suggest that ICS is effective for asthma in most athletes. However, certain asthmatic athletes are less responsive to ICS than expected. The pathogenesis in these subjects may differ from that of conventional asthma characterized by chronic allergic airway inflammation.



## Introduction

Exercise is well established as one of the factors associated with asthma exacerbation, and approximately 70–80% of asthma patients experience exercise-induced bronchoconstriction (EIB).[1] A higher prevalence of bronchial asthma has been reported in athletes than in the general population. The percentage of Olympic athletes diagnosed with asthma by a bronchial dilatation test or provocation test was 21.2% (2000) and 20.7% (2004), respectively, which was significantly higher than the rate in the general population.[2,3] Several reports describe an increased risk of developing airway hyperresponsiveness (AHR) in cross-country skiers, swimmers, and skaters.[4,5] Another investigation reported that endurance sports such as cycling and marathon running, which require substantial increases in ventilation, are high-risk sports for developing AHR.[6,7]

Inhaled corticosteroid (ICS) treatment is recommended for management of asthma in the athlete population as well as in the

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general population.[8] We have previously reported that monotherapy with ciclesonide (CIC), a new ICS administered once daily as a pro-drug type, is more effective for symptom control and reduction of fraction of exhaled nitric oxide (FeNO) than monotherapy with montelukast, a leukotriene modifier administered once daily.[9] Another study showed minimal effects of ICS in amelioration of respiratory symptoms and AHR to methacholine in cross-country skiers.[10] However, few reports have analyzed asthma treatment in the athlete population in clinical practice.

In practice, asthma is diagnosed on the basis of at least one symptom such as dyspnea, cough, chest tightness, or stridor; obstructive impairment of lung function reversible by a bronchodilator; bronchial hypersensitivity; and evidence of airway allergic inflammation (such as sputum eosinophilia and high FeNO). The International Olympic Committee (IOC) Medical Commission has provided guidelines on the diagnosis and management of asthma and EIB in athletes.[11] Bronchial provocation tests are highly recommended for diagnosis of asthma and EIB not only to support the health of athletes but also to avoid doping allegations.

Few data are available regarding responses to ICS for asthma in the athlete population. To clarify the therapeutic effects of ICS against athlete asthma, we conducted a retrospective review of the effects of ICS in Japanese athletes with asthma who were positive in at least one bronchial provocation test. The subjects were evaluated according to improvement of clinical symptoms, pulmonary function parameters, and FeNO. We conducted comparisons among sports types and between ICS responders and non-responders.

## Methods

### *Subjects*

Eighty athletes (59 men) who were nonsmokers and diagnosed with asthma at the Niigata Institute for Health and Sports Medicine were enrolled in this retrospective analysis. Athletes with respiratory symptoms as well as positive findings on a bronchodilator test or bronchial provocation test such as methacholine, exercise, or hypersaline provocation were diagnosed as asthmatic. Athletes in this study were defined as people who were competitive at the regional to national level and trained approximately 20 h/week. Sport activities were categorized as endurance/non-endurance, winter/summer, and indoor/outdoor sports according to the work of Alatanta et al.[12] This study was performed in accordance with the Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki, and with the approval of the Ethics Committee of Niigata Institute for Health and Sports Medicine.

### *Study*

Before the start of ICS treatment, all subjects underwent physical examination; pulmonary function testing; fraction of exhaled nitric oxide (FeNO); peripheral blood eosinophil count; sputum eosinophil count (if possible); total IgE; and a radioallergosorbent test (RAST) for mite, ragweed, and cedar pollen. Pulmonary function testing was performed using a spirometer (SpiroSift SP-470; Fukuda Denshi, Tokyo, Japan) in accordance with the ATS guidelines.[13] In the bronchodilator test, a positive response was defined as an increase of at least 12% in $FEV_1$ and 200 mL above the baseline value after inhalation of salbutamol (200 μg). FeNO was measured using an NO analyzer (Kimoto Denshi, Osaka, Japan) with the online method; the method of measuring FeNO conformed to a previous mutual consensus statement from the ATS/ERS.[14]

Subjects who were treated with ICS alone at a dose equivalent to 400 (<15 years of age) or 800 (≥15 years of age) μg/day of budesonide for at least 3 months were enrolled in this study. Clinical symptoms, results of pulmonary function testing, and FeNO after ICS treatment were compared with those at baseline.

### *Assessment*

The response to ICS was assessed using the physician's Global Evaluation of Treatment Effectiveness (GETE),[15,16] an overall clinical evaluation of asthma control from 12 to 24 weeks, based on all available information including patient interview and physical examination. In the GETE, treatment is rated as excellent (complete control of asthma), good (marked improvement of asthma), moderate (discernible but limited improvement of asthma), poor (no appreciable change in asthma symptoms), or worsening of asthma. Subjects with excellent, good, and moderate responses were considered responders.

### *Bronchial provocation tests*

The methacholine challenge involved 2 min of tidal breathing of methacholine, and the concentration of methacholine that provoked a 20% or more decrease in $FEV_1$ ($PC_{20}$) was determined.[17] A $PC_{20}$ of ≤8 mg/mL was defined as a positive response in this study. EIB was diagnosed as previously described.[17] Briefly, the athletes were instructed to run for 8 min at submaximal exercise intensity on a motor-driven treadmill. $FEV_1$ was measured before running and 3, 5, 10, 15, and 20 min after running. A 10% decrease in $FEV_1$ relative to the value before exercise was defined as a positive response. The hypertonic saline challenge was performed as described previously.[18] Briefly, hyperosmolar saline (4.5%) was inhaled during tidal breathing as a wet aerosol generated by a large-volume ultrasonic nebulizer. $FEV_1$ was measured before inhalation and 3, 5, 10, 15, and 20 min after inhalation. A 15% decrease in $FEV_1$ relative to the value before inhalation was defined as a positive response.

### *Statistical analysis*

The results were expressed as mean (±SD) in normally distributed data and as medians (25th–75th interquartile range) in non-normally distributed data for continuous variables. The differences between dichotomous variables were analyzed by Fisher's exact test or Mann–Whitney *U* test. The in-group (pre- and post-treatment) comparisons were made using Wilcoxon's signed-rank test. Multivariate analysis was used to identify the variables that influenced the ICS response. The data for FeNO, $PC_{20}$, IgE, and blood eosinophil count became normally distributed after log transformation. Variables that were statistically significant in the dichotomous analysis were first applied in stepwise selection because of strong correlation among the values of FeNO, $PC_{20}$, IgE, and blood eosinophil count. All variables that correlated at $p < 0.20$ in stepwise selection were applied in multivariable logistic regression analysis. All statistical analyses were performed using JMP statistical software (JMP 10.0; SAS Institute Inc., Cary, NC, USA). In all statistical analyses, $p < 0.05$ was considered significant.

## Results

Eighty athletes who had a positive response to a bronchodilator or bronchial provocation test were analyzed in this study. The baseline data of all subjects are shown in Table 1. The distribution of sports type was 35.0% in winter sports, 27.5% in endurance sports, and 31.3% in indoor sports. The baseline data of each sport type were not apparently different (data not shown). Approximately half of the subjects were diagnosed with asthma by the methacholine provocation test. The GETE assessment was collected from all

**Table 1**
Clinical characteristics.

| | |
|---|---|
| Sex (M/F) (*n*) | 59/21 |
| Age (yr) median (25th–75th quartile) | 16.0 (15–17) |
| Sports | |
| Winter (%) | 35.0 |
| Endurance (%) | 27.5 |
| Indoor (%) | 31.3 |
| Provocation test | |
| Bronchodilator (%) | 18.8 |
| Methacholine (%) | 53.8 |
| Exercise (%) | 22.5 |
| Hyperosmolarity (%) | 16.3 |
| Asthma in childhood (%) | 58.2 |
| Allergic rhinitis (%) | 64.6 |
| $Log_{10}$ serum total IgE (IU/L) mean (SD) | 2.38 (0.74) |
| Positive rate of mite-specific IgE (%) | 67.5 |
| Positive rate of cedar pollen-specific IgE (%) | 54.5 |
| Positive rate of ragweed-specific IgE (%) | 14.3 |
| $Log_{10}$ blood eosinophils (/uL) mean (SD) | 2.32 (0.36) |
| Sputum eosinophils (%) median (25th–75th quartile) | 4.6 (2.2–18.4) |
| $Log_{10}$ FeNO (ppb) mean (SD) | 1.65 (0.43) |
| %$FEV_1$ (%) mean (SD) | 92.1 (12.3) |
| $FEV_1$/FVC (%) mean (SD) | 83.9 (8.4) |
| %MMF (%) mean (SD) | 90.9 (25.7) |
| ICS (mg/d) median (25th–75th quartile) (equivalent to budesonide) | 800 (800–800) |
| Treatment duration (days) median (25th–75th quartile) | 147 (112–196) |
| GETE (excellent/good/moderate/poor/worsening) (*n*) | 15/37/15/11/2 |

FeNO, fraction of exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; MMF, maximum mid expiratory flow rate; ICS, inhaled corticosteroid; GETE, global evaluation of treatment effectiveness.

patients from 12 to 24 weeks. From the GETE results, 83.8% of patients were considered responders to ICS (excellent, 18.8%; good, 46.2%; moderate, 18.8%) and 16.2% non-responders (poor, 13.7%; worsening, 2.5%).

In Table 2, the changes in the indices after ICS therapy are compared according to the results of the GETE. In the responders to ICS, logarithm to the base 10 ($log_{10}$) FeNO (pretreatment: 1.69 ± 0.43 ppb; posttreatment: 1.49 ± 0.32 ppb; $p < 0.0001$), $FEV_1$ (% predicted) (91.4% ± 12.6%, 95.9% ± 12.9%; $p = 0.0002$), $FEV_1$/FVC (84.9% ± 8.4%, 86.8% ± 7.5%; $p = 0.0027$), and MMEF (% predicted) (91.4% ± 24.0%, 101.5 ± 28.4%; $p = 0.0003$) significantly improved after treatment, whereas there were no significant changes after treatment in non-responders to ICS (Table 2). Among sports types, there were no differences in GETE results, changes of respiratory functions, or $log_{10}$ FeNO (data not shown).

Athletes with an effective clinical response to ICS displayed higher values than athletes with an ineffective response to ICS in the following parameters: Th2-associated biomarkers such as serum total IgE, blood eosinophil count, and FeNO ($log_{10}$ IgE: responders versus non-responders, 2.51 ± 0.71 IU/L versus 1.61 ± 0.63 IU/L, $p < 0.0001$; $log_{10}$ eosinophil count: 2.37 ± 0.36/μL versus 2.08 ± 0.34/μL, $p = 0.0181$; $log_{10}$ FeNO: 1.69 ± 0.43 ppb versus 1.40 ± 0.39 ppb, $p = 0.0411$), as well as $FEV_1$/FVC (responders versus non-responders, 85.0% ± 8.2% versus 77.9% ± 7.2%, $p = 0.0053$). In addition, responders had lower logarithm to the base 2 ($log_2$) $PC_{20}$ values than non-responders (responders versus non-responders, 0.09 ± 1.37 mg/mL versus 1.28 ± 1.06 mg/mL, $p = 0.0200$). In sputum eosinophils, the data exhibited high variability; therefore, significant differences were not observed among groups. There were negligible differences in treatment duration and ICS dose (Table 3).

To identify the variables that influenced the ICS response, we performed multivariate statistical analysis. Firstly, the variables that were statistically significant in the dichotomous analysis were applied in stepwise selection because the data of $log_{10}$ FeNO, $log_{10}$ IgE, $log_2$ $PC_{20}$, and $log_{10}$ eosinophil count were strongly correlated with each other. The stepwise selection revealed that $FEV_1$/FVC and $log_{10}$ IgE were useful independent variables. According to multivariate logistic analysis, both $FEV_1$/FVC (odds ratio (OR), 1.14; 95% confidence interval (95% CI), 1.04–1.28; $p = 0.0048$) and $log_{10}$ IgE (OR, 5.71; 95% CI, 2.24–18.40; $p = 0.0001$) were identified as independent factors with a significant association with the ICS response (Table 4).

## Discussion

Although many reports have described a higher prevalence of asthma in the athlete population, detailed investigations on the pharmacological management of asthma in athletes are lacking. We previously reported that ciclesonide, as a once-daily pro-drug ICS, was superior for improvement of symptoms, pulmonary function, and FeNO relative to the leukotriene modifier, montelukast.[9] In this study, we retrospectively investigated the effects of ICS and differences between ICS responders and non-responders among Japanese athletes diagnosed with asthma by a bronchodilator or bronchial provocation test. Although this study was retrospective in design and may thus be affected by variable dosing of ICS, potential effects of non-adherence, or lack of randomization, this is the first report to analyze the ICS response in an athlete population in a practical setting.

ICS is the most effective drug for long-term control of asthma and prevention of EIB.[19] The guidelines for management of asthma in athletes also describe ICS as a first-line agent.[20] In subjects with airway inflammation consistent with asthma, the benefit of ICS treatment in reducing the severity of EIB is well established.[21] However, the only long-term study performed in athletes with EIB suggests that daily treatment with ICS does not have any beneficial effect on respiratory symptoms or AHR to methacholine.[10] In this study, ICS was effective in most of the athletes for amelioration of clinical symptoms, reduction of FeNO values, and improvement of pulmonary function parameters. However, approximately 15% of the athletes were not responsive to ICS. Previous reports and the data of the present study indicate that the phenotypes of asthma in the athlete population are heterogenous.[22–24]

In the athletes in this study, a positive response to ICS was associated with higher IgE and higher $FEV_1$/FVC in multivariate

**Table 2**
Summary of groups for response to ICS treatment.

| Responder (65) | | | | Non-responder (15) | | | |
|---|---|---|---|---|---|---|---|
| | Pretreatment | Posttreatment | *p* value | | Pretreatment | Posttreatment | *p* value |
| $Log_{10}$ FeNO (ppb) | 1.69 (0.43) | 1.49 (0.32) | $p < 0.0001^{**}$ | $Log_{10}$ FeNO (ppb) | 1.40 (0.39) | 1.55 (0.30) | $p = 0.1264$ |
| %FEV (%) | 91.4 (12.6) | 95.9 (12.9) | $p = 0.0002^{**}$ | %FEV (%) | 95.5 (12.6) | 91.3 (9.5) | $p = 0.1598$ |
| FEV/FVC (%) | 84.9 (8.4) | 86.8 (7.5) | $p = 0.0027^{*}$ | FEV/FVC (%) | 77.6 (8.2) | 80.0 (7.8) | $p = 0.1763$ |
| %MMF (%) | 91.4 (24.0) | 101.5 (28.4) | $p = 0.0003^{**}$ | %MMF (%) | 83.6 (33.5) | 79.9 (29.5) | $p = 0.5669$ |

FeNO, fraction of exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; MMF, maximum mid expiratory flow rate.
Data express mean (SD) or median (25th–75th quartile). Asterisks indicate significance between pretreatment and posttreatment ($^{*}p < 0.05$, $^{**}p < 0.001$).

**Table 3**
Summary of responder and non-responder to ICS treatment.

| | Responder | Non-Responder | *p* value |
|---|---|---|---|
| Sex (M/F) | 47/20 | 12/1 | $p = 0.1665$ |
| Age (yr) median (25th–75th quartile) | 16.0 (15.0–17.0) | 16.0 (15.0–17.5) | $p = 0.1619$ |
| Winter (%) | 36.9 | 30.8 | $p = 0.7607$ |
| Endurance (%) | 22.4 | 23.1 | $p = 1.0000$ |
| Outside (%) | 71.6 | 53.8 | $p = 0.3260$ |
| Symptom at rest (%) | 17.9 | 23.1 | $p = 0.7018$ |
| Symptom on exercise (%) | 91.0 | 69.2 | $p = 0.0517$ |
| Asthma in childhood (%) | 60.6 | 46.2 | $p = 0.3699$ |
| Allergic rhinitis (%) | 68.2 | 46.2 | $p = 0.2030$ |
| $Log_{10}$ IgE (IU/L) mean (SD) | 2.51 (0.71) | 1.61 (0.63) | $p < 0.0001$* |
| Positive rate of mite-specific IgE (%) | 73.4 | 38.5 | $p = 0.0222$* |
| Positive rate of cedar pollen-specific IgE (%) | 60.9 | 23.1 | $p = 0.0159$* |
| Positive rate of ragweed-specific IgE (%) | 15.6 | 7.7 | $p = 0.6785$ |
| $Log_{10}$ eosinophil count (/uL) mean (SD) | 2.37 (0.36) | 2.08 (0.34) | $p = 0.0181$* |
| Sputum eosinophils (%) median (25th–75th quartile) | 5.9 (2.8–18.8) | 1.1 (0.0–2.6) | $p = 0.2704$ |
| $Log_{10}$ FeNO (ppb) mean (SD) | 1.69 (0.43) | 1.40 (0.39) | $p = 0.0411$* |
| $Log_2$ $PC_{20}$ (mg/mL) mean (SD) | 0.09 (1.37) | 1.28 (1.06) | $p = 0.0200$* |
| %$FEV_1$ (%) mean (SD) | 91.4 (12.2) | 88.1 (13.3) | $p = 0.3146$ |
| $FEV_1$/FVC (%) mean (SD) | 85.0 (8.2) | 77.9 (7.2) | $p = 0.0053$* |
| %MMF (%) mean (SD) | 92.7 (24.4) | 81.4 (30.0) | $p = 0.1490$ |
| Treatment duration (days) median (25th–75th quartile) | 147.0 (112.0–185.0) | 168.0 (124.5–223.5) | $p = 0.2137$ |
| ICS (mg/d) mean (25th–75th quartile) | 800.0 (800–800) | 800.0 (800–800) | $p = 0.8940$ |

FeNO, fraction of exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; MMF, maximum mid expiratory flow rate; $PC_{20}$, provocative concentration causing a 20% fall in $FEV_1$; ICS, inhaled corticosteroid.
Data express mean (SD) or median (25th–75th quartile). Asterisks indicate significance between responder and non-responder(*$p < 0.05$).

statistical analysis. Similar to our data, previous reports have described that the response to steroid therapy in asthma patients is associated with IgE level.[25] Hyperresponsiveness to methacholine,[26] the levels of FeNO,[27,28] and eosinophil count in peripheral blood[25] have also been reported as predictors of the response to ICS. In the present study, the values of FeNO, IgE, $PC_{20}$, and blood eosinophil count were mutually correlated, so these parameters were possible confounding factors. Interestingly, our data indicated that subjects with higher $FEV_1$/FVC were more responsive to ICS, whereas previous studies reported that severe obstructive impairment of pulmonary function was a predictive factor for the response to ICS.[29,30] Although the odds ratio of $FEV_1$/FVC indicates a slight contribution, this parameter definitely plays a role in ICS response. These data may reflect discordance between airway allergic inflammation and airway obstruction in asthma in the athlete population.

We described the characteristics of non-responders to ICS, which included lower levels of Th2-associated biomarkers, lower $FEV_1$/FVC, and mild airway hyperresponsiveness. These characteristics are also seen in the non-athlete adult population; however, they are often complicated with COPD or obesity, which were unlikely in our population. Recently, some reports have described that the pathophysiological mechanisms of athlete asthma involve airway epithelial damage and mechanical stress caused by hyperpnea.[4,22,24] The onset of asthma after starting strenuous exercises and the non-allergic phenotype appeared to be clinically important for distinguishing the patients from those with conventional allergic asthma. However, there were no any differences in the prevalence of childhood asthma and allergic rhinitis in this study.

**Table 4**
Multivariate logistic analysis of ICS response in $FEV_1$/FVC and $log_{10}$ IgE.

| | Odds ratio (95% confidence interval) | *p* value |
|---|---|---|
| $FEV_1$/FVC | 1.14 (1.04–1.28) | 0.0048* |
| $Log_{10}$ IgE | 5.71 (2.24–18.40) | 0.0001* |

$FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity. Asterisks indicate significance (*$p < 0.05$).

In this study, the GETE rating was used to classify subjects as responders or non-responders to ICS. Certain previous studies classified subjects as responders if the GETE rating was excellent or good.[15,16] In our study, subjects with excellent, good, and moderate GETE ratings were classified as responders because the aim of this study was to identify and investigate the population in which ICS was not at all effective. However, precise evaluation of the responsiveness to ICS might have been limited by the use of the GETE for the assessment. In previous studies, the proportion of ICS responders was reported as 40–60%[29–31] in the non-athlete population, whereas our study reported a proportion of 85%. These discrepancies may have resulted from differences in the definition of ICS responders. In the previous studies, subjects with an improvement in $FEV_1$ of 5–7.5% compared with that before treatment were considered responders. In contrast, we only determined the results on the basis of the GETE rating.

Subjects in this study were exclusively athletes diagnosed with asthma by the bronchodilator or bronchial provocation test. The International Olympic Committee (IOC) medical conference has highly recommended the bronchial provocation test for diagnosis of asthma considering anti-doping strategies and athlete health.[11] Certain athletes, particularly in winter sports, display discrepancies between clinical symptoms and airway hyperresponsiveness; that is, they have certain symptoms of asthma without airway hyperresponsiveness.[5] In another study, 61% of EIB-positive athletes and 45% of normal pulmonary function athletes reported symptoms related to EIB _ENREF_33.[32] According to these data, self-reported symptoms are unlikely reliable for diagnosis of asthma in athletes.

In summary, we conducted a retrospective analysis of ICS treatment in Japanese athletes with asthma. Most of the athletes showed better control of symptoms, improved pulmonary function parameters, and decreased FeNO value. However, certain athletes showed a minimal response to ICS clinically, in addition to lower Th2-associated biomarker levels, lower $FEV_1$/FVC, and higher $PC_{20}$. In multivariate statistics, $FEV_1$/FVC and $log_{10}$ IgE were independently associated with the ICS response. These data suggest that the phenotypes of asthma among athletes are heterogenous, and the pathogenesis in the subtype that does not respond to ICS may differ from that of typical chronic allergic airway inflammation.

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*Conflict of interest*
The authors have no conflict of interest to declare.

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